Office Action Summary	Application No.	Applicant(s)	
	10/805,650	BORNS, MICHAEL	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/03/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-18,21-29 and 40-52* is/are pending in the application.

4a) Of the above claim(s) *12,14,16-18 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 13,15,25-29 and 40-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's submission of new claims 40-52 in the paper filed on 05/01/2008 is acknowledged.

Claims 1-10, 13, 15, 25-29, and 40-52 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn In Part

Claim Rejections Withdrawn In Part - 35 USC § 112 First Paragraph

2. The rejection of claims 1-10, 13, 15, 25-29, and 40 under 35 U.S.C. 112, first paragraph, is withdrawn in part. Applicant's argument is persuasive that the specification provides one example in evidence in Figure 6 and its description on p. 30 that a polymerase fusion protein which is chimeric Pfu-Sso7d DNA polymerase produces amplicons at pH 10.0 and 11.8. Weighing this evidence and the conventions of significant figures the claimed inventions with regards to a chimeric Pfu-Sso7d DNA polymerase is enabled for the pH range of 9.3 to 12.

It is further noted that Figure 2 which Applicant also cites is not solely giving results of a polymerase fusion protein but of a blend of a polymerase fusion protein which is chimeric Pfu-Sso7d DNA polymerase and another polymerase (non-fused). Thus the results of Figure 2 are confounded and no evidence is provided that the amplicon produced is a result of the polymerase fusion protein.

The pH range of greater than pH 12 to pH 14 is not enabled for previously presented claims and new claims 49 and 50 as given below

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Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 112, First Paragraph

3. The rejection of claims 1-10, 13, 15, 25-29, and 40-46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement by not reciting blends of polymerases is withdrawn. Applicant's arguments are persuasive that one embodiment of the invention is to blends of polymerases and another embodiment of the invention is to a polymerase fusion protein alone, that is not in a blend of polymerases.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The rejection of claims 1-10, 13, 15, 25-29, and 40-46 under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention by not reciting blends of polymerases is withdrawn. Applicant's arguments are persuasive that one embodiment of the invention is to blends of polymerases and another embodiment of the invention is to a polymerase fusion protein alone, that is not in a blend of polymerases.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 103

5. The rejection of claims 1-4, 7-11, 13, 15, 19, 25-30, and 40-46 under 35 U.S.C. 103(a) as being unpatentable over Wang (2001) is maintained. Applicant's arguments filed 06/03/2008 have been fully considered but they are not persuasive.

Applicant argues that Wang does not teach a fusion protein in a reaction buffer at pH 9.0. However, the teachings of Wang on this point vary as Wang does teach: "The reaction buffer for Pfu-Sso7d [fusion protein] contains [sic] was performed using DyNAzyme EXT buffer (see Example 6-2) . . . " and teaches: "Specific amplicons of expected sizes were amplified by both Pfu-Sso7d and Taq polymerase Example 6-2) . . . " (see page 42, 3rd and 6th sentences). Contrary to this in Example 6-2, Wang teaches the reaction buffer for the Pfu-Sso7d fusion protein was pH 8.8. Applicant has already confirmed that DYNAZYME EXT buffer is pH 9.0 (see Wang at p. 40 line 14). Thus, Wang does teach at least pH 8.8 for the Pfu-Sso7d fusion polymerase and for the Taq polymerase (see 2nd sentence on p. 42) and teaches pH 9.0 for polymerases of DYNAZYME EXT.

In response to Applicant's argument that one of ordinary skill in the art would not be motivated to perform the method at pH 9.5, it was known in the art that polymerases function at pH 9.5 and up to pH 10, as evidenced by Dietrich et al. (2002) and as further discussed in section 8 below. The teaching of Dietrich et al. (2002) also support, as given below, that polymerase activity can be found over a broad pH range of pH 7 to pH 10 which is consistent with the teachings of Wang. Thus Applicant's opinion that

one of ordinary skill in the art would not have expected the polymerase fusion of Wang to function at pH 9.5 is not supported by the teachings of the prior art.

Applicant also argues that the blend of a fusion polymerase Pfu-Sso7d and *Pfu* polymerase has the same property of the fusion polymerase Pfu-Sso7d which is activity at high pH. However, the blend as claimed of a fusion polymerase Pfu-Sso7d and *Pfu* polymerase does not have any practical significance over a sole fusion polymerase Pfu-Sso7d and does not show a result which is greater than the sum of the effects taken separately; here the sum of the effect of the blend has not been shown to be greater than the individual effects of a fusion polymerase Pfu-Sso7d and *Pfu* polymerase. There is no demonstration of "synergism" (see MPEP 716.02(a) I).

6. The rejection of claims 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Wang (2001) and further in view of Sanger et al. (1977) is maintained. Applicant's arguments filed 12/17/2007 have been fully considered but they are not persuasive.

Applicant argues that as the rejection over Wang should be withdrawn that the rejection over Wang in view of Sanger et al. should be withdrawn. However, the rejection over Wang is maintained and thus the rejection over Wang in view of Sanger et al. is maintained.

New Rejections Necessitated by Amendment

New Claim Rejections - 35 USC § 103

7. Claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (2001).

Wang teaches as noted above and in previous Office Actions.

Regarding claims 47 and 48, Wang teach blends/mixtures of polymerases (see p. 2 line 3) including Taq and *Pfu* and the blend which is DYNAZYME EXT (SEE Example 6-2).

Regarding claims 47 and 48, Wang does not specifically teach a blend comprising a DNA polymerase fusion and a second DNA polymerase and where that second DNA polymerase is *Pfu*. While it is noted that Wang teaches the fusion polymerase Pfu-Sso7d is more efficient than some blends (see p. 40 line 29), from the teaching of Wang it is expected that a blend of fusion polymerase Pfu-Sso7d and *Pfu* polymerase would have functioned in the claimed method, as Wang teaches both polymerases function at high pH (See example 6-1). Thus the blend of fusion polymerase Pfu-Sso7d and *Pfu* polymerase for use in the claimed method would have been obvious from the teachings of Wang.

Furthermore, the blend as claimed of a fusion polymerase Pfu-Sso7d and *Pfu* polymerase does not have any practical significance over a sole fusion polymerase Pfu-Sso7d and does not show a result which is greater than the sum of the effects taken separately; here the sum of the effect of the blend has not been shown to be greater

than the individual effects of a fusion polymerase Pfu-Sso7d and *Pfu* polymerase. There is no demonstration of "synergism" (see MPEP 716.02(a) I).

8. Claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (2001) and Dietrich et al. (2002).

Wang teaches as noted above and in previous Office Actions.

Regarding claims 49 and 50, Wang teaches where the Sso7d-Taq fusion protein decreased extension time for a 5kb fragment of at least 5 minutes over the extension time of the wild type Pfu polymerase by teaching:

> "The results showed that a Pfu-Sso7d fusion protein was able to amplify both the 1 kb and 5 kb fragments using a 1 min extension time, and was also able to amplify the 10 kb fragment using a 5 rnin extension time. In contrast, Pfu polymerase amplified only the 1 kb fragment using either a 1 min or a 5 min extension time" (see p. 39 lines 19-23).

Regarding claims 51 and 52, Wang teaches using the Pfu-Sso7d fusion polymerase protein at pH 8.8 and teaches using polymerase at pH 9.0 (see Example 6-2).

Wang does not specifically teach using the Pfu-Sso7d fusion polymerase protein at the pH range of 9.5 to 12.

Regarding claims 51 and 52, Dietrich et al. teach that a recombinant modified polymerase had more activity at pH 9.5 in CAPS buffer and retained 80% of its optimal activity in Tris buffer in the pH range of 7 to 10 (see first two sentences in 1st column on p. 92).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods for a modified polymerase of Wang by using a higher pH as suggested by Dietrich et al. with a reasonable expectation of success. The motivation to do so is provided by Dietrich et al. who teach recombinant modified polymerases can have more activity at pH 9.5 and can retain more than 80% of optimal activity over a broad pH range of 7 to 10. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Furthermore Wang teaches using a DNA polymerase fusion at pH 8.8 (see p. 29, line 14) and polymerase blend at pH 9.0 (see p. 40, line 14). Thus as Wang teaches different alkaline pH's are useful for DNA polymerases, it would have been obvious to optimize pH. Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the claimed pH of 9.5 and above as used by the applicant or in the range of pH 9.0 as used by Wang since these differences in pH would not be expected to greatly alter the conditions for amplification. One of ordinary skill in the art would have not expected that the activity of a DNA polymerase fusion would be completely lost at pH 9.5 when it was functional at pH 9.0. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties."

Thus, an ordinary practitioner would have recognized that the droplet size could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Routine optimization is not considered inventive and no evidence has been presented that the selection of pH 9.5 was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art of pH 9.0. As noted, a skilled artisan would expect a pH of 9.0 to have nearly identical properties in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results especially in view of the teachings of Dietrich et al. as given above.

Claim Rejections - 35 USC § 112 First Paragraph

9. Claims 1-10, 13, 15, 25-29, 40, 49, and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a range of pH 9.3 to 11.8, does not reasonably provide enablement for a range of greater than pH 12 to pH 14. Also the specification while being enabling at pH of 9.3 to 11.8 for one specific fusion protein (SEQ ID NO: 126) comprising a *Pyrococcus furiosus* polymerase and an Sso7d DNA binding domain, does not reasonably provide enablement for any fusion protein comprising a *Pyrococcus furiosus* polymerase and an Sso7d DNA binding domain . The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. One of skill in the art would not know how to overcome the art recognized problem of protein hydrolysis at high pH with other than the fusion of SEQ ID NO: 126. One of skill in the art would not know how to make the claimed fusion protein with the claimed property of functioning at high pH.

The nature of the invention and breadth of claims

Base claims recite synthesizing DNA with a protein fusion polymerase in the pH range of 9.3 to 14. In fact the specification does not disclose that the fusion polymerase will operate above pH 11.8.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there the art teaches that protein hydrolyses at pH 10 and higher. Ernster (United States Patent 4,545,933 issued 1985, previously cited) teaches that proteins are hydrolyzed at pH 10 and higher (see claims 9 and 19). Hugli et al. further teach that complete hydrolysis of proteins can be achieved with alkaline hydrolysis (see Title, Summary, and see 1st sentence of the last paragraph on p. 2828) especially with 4.2 N NaOH (see Table 1) which is at least pH 13.8. That 4.2 N NaOH is at least pH 13.8 is evidenced by Drazic et al. (1999) who teach that 1 M NaOH which is 1 N NaOH has a pH of 13.81 (see 1st sentence of 3rd paragraph in the 2nd column on p. 161).

Working Examples

The specification has no working examples of synthesizing DNA in the pH range of 12 to 14 with a protein fusion polymerase.

Guidance in the Specification.

The specification provides no evidence that the disclosed protein fusion polymerase would be able to function in pH range of greater than pH 12 to pH 14.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, given the broad claims in an art which teaches opposite of the claims, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written, if in fact, it were possible.

Conclusion

10. No claim is free of the prior art.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
August 13, 2008

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637